Original Article

The prognostic value of 4.1 mRNA expression in non-small cell lung cancer

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Background: The mechanism of 4.1 family in human cancer has not been elucidated. In this study we investigate the value as a prognostic factor of mRNA expression of 4.1 family in non-small cell lung cancer (NSCLC).

Methods: A survival analysis was carried out through the Kaplan-Meier plotter (KM plotter) database. KM's method was used to estimate the prognostic value of 4.1 mRNA expression in NSCLC.

Results: Expression of four members are linked to overall survival (OS) in NSCLC patients, among which 4.1G, 4.1B, 4.1R are concerned with first progression (FP), and 4.1G, 4.1R are correlated with post progression survival (PPS) besides. Only 4.1B expression is associated with OS in squamous cell carcinoma, as four members with OS in adenocarcinoma. What's more, 4.1G, 4.1N high mRNA are linked to better FP in adenocarcinoma, and 4.1R overexpression is linked to better PPS. The expression of 4.1G is associated with the prognosis in female, whereas 4.1R in male. Furthermore, 4.1G and 4.1B play as protective roles in non-smoking populations, while 4.1N overexpression is related to poorer PPS. All the four family members are associated with early stage in NSCLC 4.1G, 4.1B and 4.1R are closely related to surgical resection, yet 4.1N has no prognostic significance in patients receiving treatments. However, the results need to be verified in clinical trials further.

Conclusions: Our results offer new opinion about the prognostic value of 4.1 protein family in NSCLC, which may contribute to the development of new therapy for NSCLC.

Keywords: 4.1 mRNA; prognosis; non-small cell lung cancer (NSCLC); Kaplan-Meier plotter (KM plotter)

Submitted Jul 09, 2020. Accepted for publication Jan 22, 2021.
doi: 10.21037/tcr-20-2501
View this article at: http://dx.doi.org/10.21037/tcr-20-2501

Introduction

Lung cancer is the leading cause of mortality in both female and male, and a total of 234,030 new cases and 154,050 mortalities are estimated to occur in the United States in 2018 (1). Lung cancer is classified as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and NSCLC accounts for 80–85% of the total cases (2). Even though a great number of clinical trials are designed to target potential oncogenes such as *KRAS*, *BRAF*, *HER2*, *PI3KCA* and *MET* in the past decade, the 5-year overall survival (OS) has not been significantly changed (2,3). Therefore, searching for biological targets that may effectively improve therapy and prognosis is the key to the treatment of NSCLC.

The protein 4.1 family including the 4.1R (mainly expressed in red cell), 4.1N (neuron-specific expression),

4.1G (broad expression) and 4.1B (mainly in the brain), which are encoded by the *EPB41* genes, are components of the cortical cytoskeleton underlying the cell membrane (4). 4.1 proteins have conserved domains, including N-terminal FERM domain (membrane-binding domain-MBD domain), spectrin-actin binding domain (SAB domain), C-terminal domain (CTD structure domain) (5). Those domains can link to cortical cytoskeleton via binding of some cell cortex nodes, such as actin protein, spectrin, transmembrane adhesion protein and other family proteins, to regulate not only the polarity, adhesion and motility of the tissue cells, but also the trans-membrane transport. Recently, a variety of researchers have found that 4.1 protein is closely connected with the occurrence and development of tumors. It has been reported that abnormal expression of 4.1 protein exists in various types of tumors such as NSCLC, breast cancer, liver cancer and prostate cancer (6-9).

Kaplan-Meier plotter (KM plotter) (http://kmplot.com/analysis/), created by Győrffy *et al*. (10), is an online survival analysis software used to evaluate the prognostic significance of biomarkers. In this study, we used KM plotter to assess the prognostic value of mRNA expression of each member of protein 4.1 in NSCLC, and the correlation with smoking history, OS, pathological grades, clinical stages and clinical therapy.

We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2501).

Methods

Materials and data

We used KM plotter, which includes 2,437 lung cancer patients with a mean follow-up of 49 months, to determine the prognostic values of 4.1s in lung cancer.

Statistical analysis

We collected the baseline data including number of cases, histology, stage, gender, smoking history, therapeutic regimen as well as hazard ratio (HR), 95% confidence interval (CI) and log-rank P values. P<0.05 was considered statistically significant.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All data in the database is publicly available and exempt from Institutional Review Board review.

Results

Prognostic value of 4.1s in NSCLC

4.1 family members existing in NSCLC patients were found in the database (*Figure 1*). From the survival curves, we found that high level of mRNA expression of 4.1G (HR =0.75, 95% CI: 0.66–0.86, P=1.2e–05), 4.1B (HR =0.84, 95% CI: 0.74–0.95, P=0.0058), 4.1N (HR =0.8, 95% CI: 0.71–0.91, P=0.00083), 4.1R (HR =0.59, 95% CI: 0.5–0.7, P=6.2e–10) were associated with a more favorable prognosis.

Furthermore, our results showed that the overexpression of 4.1G (HR =0.73, 95% CI: 0.60–0.88, P=0.001), 4.1B (HR =0.78, 95% CI: 0.65–0.95, P=0.013), 4.1R (HR =0.54, 95% CI: 0.41–0.72, P=1e–05) were related to better FP, except 4.1N (HR =1.02, 95% CI: 0.85–1.24, P=0.81). At the same time, the high expression of 4.1G (HR =0.78, 95% CI: 0.6–1.0, P=0.049) and 4.1R (HR =0.45, 95% CI: 0.29–0.70, P=0.00023) forebode longer PPS, while overexpression of 4.1B (HR =0.88, 95% CI: 0.68–1.14, P=0.33) and 4.1N (HR =1.01, 95% CI: 0.78–1.30, P=0.96) were unrelated to PPS.

Prognostic value of 4.1 members in different NSCLC subtypes

There are two different intrinsic subtypes of NSCLC including squamous cell carcinoma and adenocarcinoma in the database (*Figure 2*). As for patients with squamous cell carcinoma, 4.1B (HR =0.78, 95% CI: 0.62–0.99, P=0.041) mRNA expression level was connected with improved OS, whereas 4.1G (HR =0.85, 95% CI: 0.67–1.08, P=0.18), 4.1R (HR =0.84, 95% CI: 0.61–1.14, P=0.25) and 4.1N (HR =0.81, 95% CI: 0.64–1.03, P=0.078) not. Furthermore, the high expression of four members were not associated with FP (4.1G: HR =0.77, 95% CI: 0.46–1.28, P=0.31; 4.1B: HR =0.84, 95% CI: 0.5–1.4, P=0.49; 4.1N: HR =0.94, 95% CI: 0.57–1.58, P=0.83; 4.1R: HR =0.82, 95% CI: 0.49–1.37, P=0.44) or PPS (4.1G: HR =1.74, 95% CI: 0.59–5.09, P=0.31; 4.1B: HR =1.29, 95% CI: 0.46–3.60, P=0.63; 4.1N: HR =1.57, 95% CI: 0.54–4.54, P=0.41; 4.1R: HR =1.03, 95% CI: 0.36–2.98, P=0.95) in squamous cell carcinoma.

In adenocarcinoma patients, however, high mRNA expression of 4.1 members (4.1G: HR =0.57, 95% CI: 0.45–0.73, P=5e–06; 4.1B: HR =0.59, 95% CI: 0.47–0.75, P=1e–05; 4.1N: HR =0.66, 95% CI: 0.52–0.85, P=8e–04) were significantly related to OS, especially the 4.1R (HR =0.4, 95% CI: 0.31–0.52, P=7.2e–13). Except 4.1B (HR =0.86, 95% CI: 0.63–1.18, P=0.35), high expression of

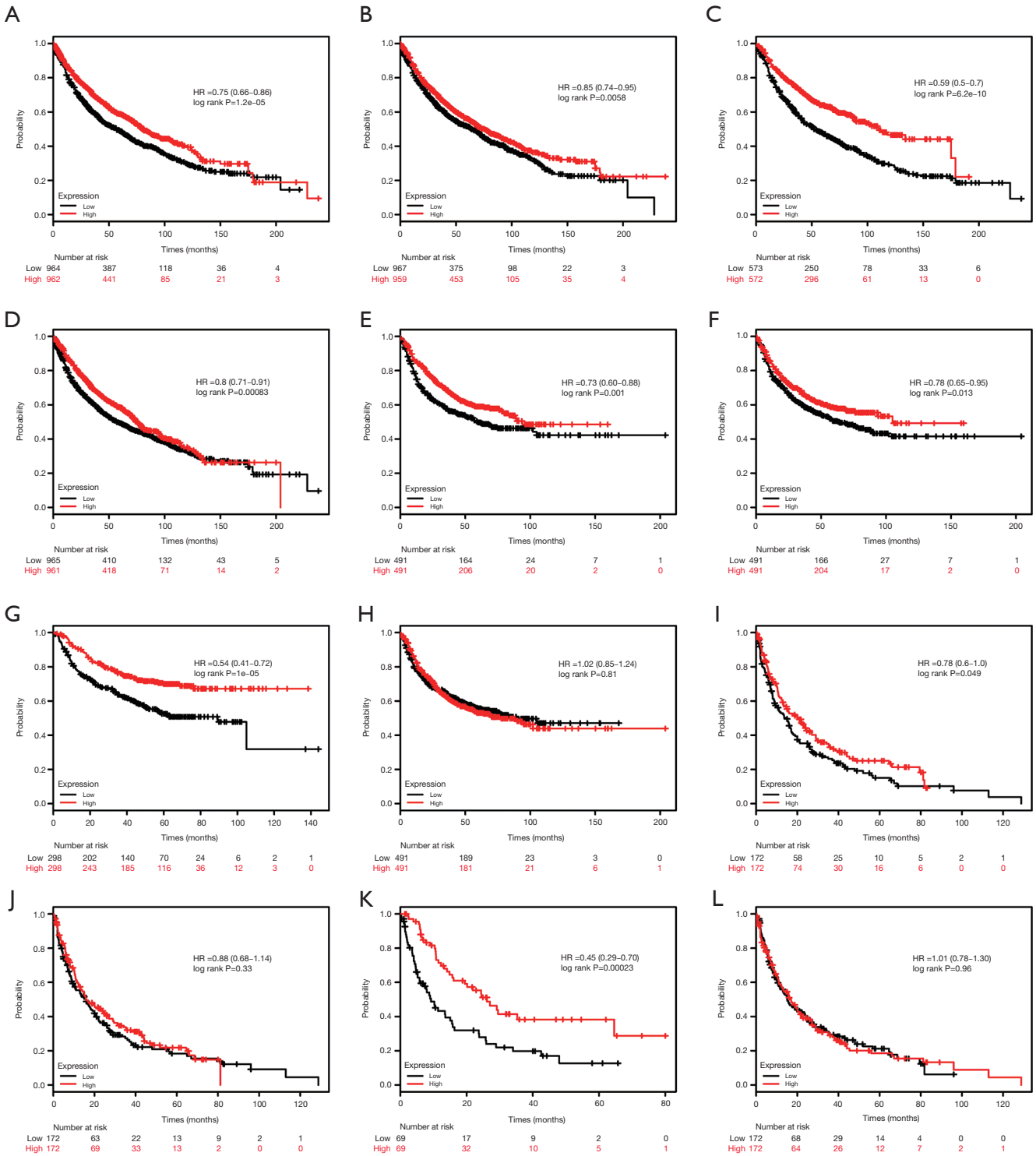

Figure 1 The prognostic roles of 4.1 in NSCLC. (A,B,C,D) High mRNA expression of 4.1G, 4.1B, 4.1R, 4.1N were significantly associated with better OS. (E,F,G,H) The relationship of 4.1G, 4.1B, 4.1R, 4.1N with FP. (I,J,K,L) The relationship of 4.1G, 4.1B, 4.1R, 4.1N with PPS. HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; FP, first progression; PPS, post progression survival.

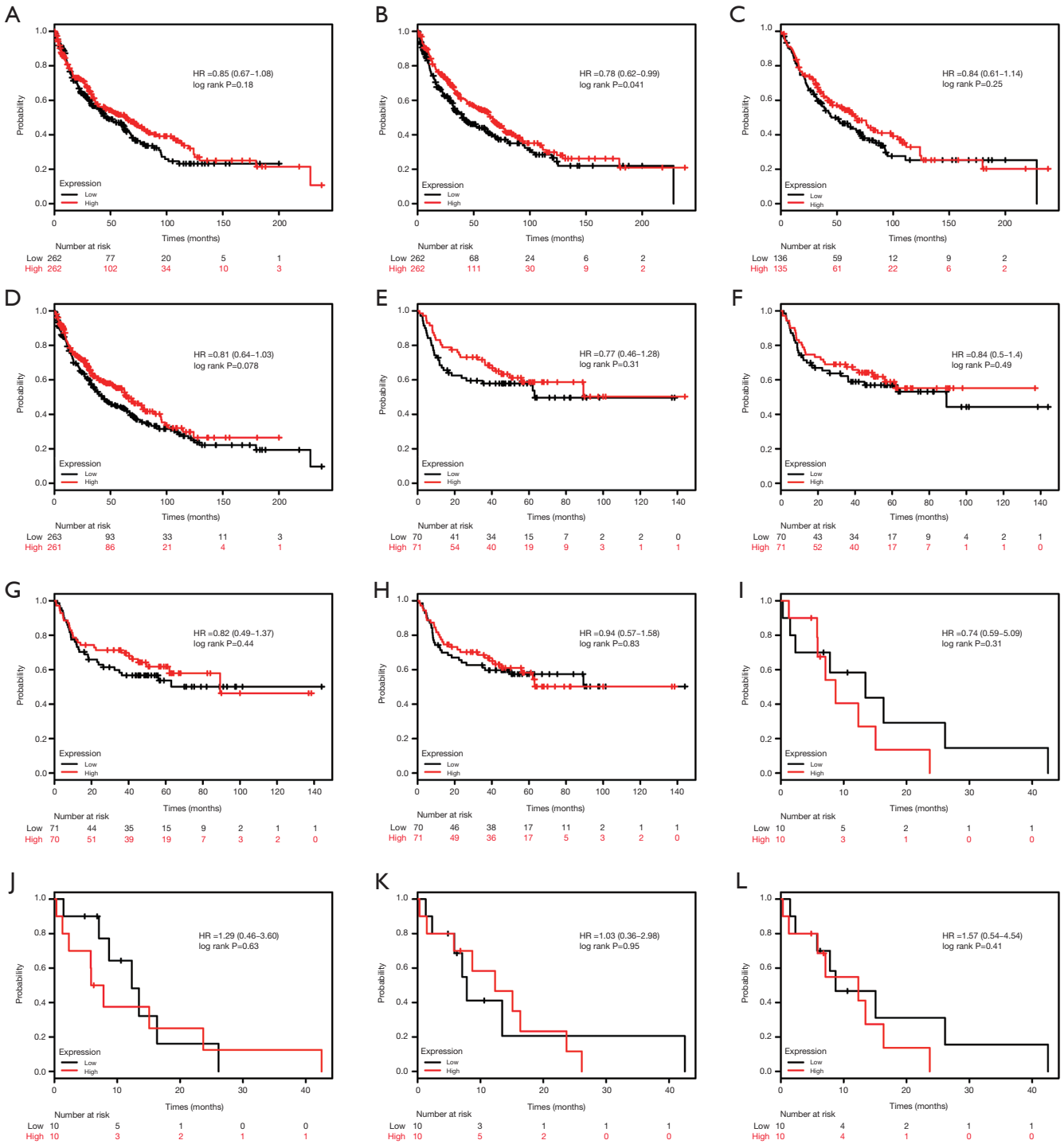

Figure 2 The prognostic roles of 4.1 in squamous cell carcinoma. (A,B,C,D) The relationship of 4.1G, 4.1B, 4.1R, 4.1N with OS. (E,F,G,H) The relationship of 4.1G, 4.1B, 4.1R, 4.1N with FP. (I,J,K,L) The relationship of 4.1G, 4.1B, 4.1R, 4.1N with PPS. HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; FP, first progression; PPS, post progression survival.

4.1G (HR =0.65, 95% CI: 0.48–0.89, P=0.0073), 4.1N (HR =0.68, 95% CI: 0.50–0.94, P=0.0017) and 4.1R (HR =0.49, 95% CI: 0.35–0.68, P=1.4e–05) were correlated with FP. However, only high mRNA expression of 4.1R (HR =0.61, 95% CI: 0.37–0.99, P=0.045) was related to PPS. All these data, to some extent, suggest that only the 4.1B high expression come along with survival benefits in squamous cell carcinoma, and the overexpression of 4.1R predicted a better prognosis in adenocarcinoma (*Figure 3*).

Prognostic values of 4.1s in NSCLC according to clinicopathological features and clinical therapy

We also explored the relationship of 4.1 members with several baseline characteristics such as gender, smoking history, pathological grades, clinical stages, and therapy regimen. The high level of 4.1G was associated with longer OS, FP and PPS in female, while 4.1G overexpression merely with better OS in male. In contrast, the high level of 4.1R was related to improved OS, FP and PPS in male. But for female, 4.1R overexpression was only connected with OS, FP. What's more, the high expression of 4.1N was found to be an essential indicator for prolonged OS in male, while 4.1B was not related to gender. Therefore, 4.1G high expression may indicate a better prognosis in female, and so does the high level of 4.1R in male though (*Table 1*).

As shown in *Table 2*, we collected and analysed the prognostic data of 4.1 family members in smokers and non-smokers. High mRNA expression of 4.1G was correlated with longer OS and FP in patients with or without smoking history and was significantly related to PPS in those without smoking history, showing that the high level of 4.1G may have a protective effect in non-smokers. Furthermore, 4.1B was more possibly linked to better OS and FP. High mRNA expression of 4.1R was correlated with improvement of OS in all population, where a better FP in patients without smoking history and a better PPS with smoking history can be observed respectively. It is worth noting that, although the 4.1 family was shown to have a protective role in population with NSCLC, high 4.1N expression was closely related to poorer PPS in those people without a history of smoking.

High mRNA expression levels of almost the whole 4.1s were associated with OS and the high expression of 4.1G, 4.1B and 4.1R were also related to better OS in patients with stage I and II lung cancer, while the 4.1N was only correlated with OS in stage I lung cancer. Regrettably, the relationship between 4.1 members and stage IV lung cancer fails to be found in the database (*Table 3*).

The 4.1G, 4.1B and 4.1R were significantly linked with better OS and FP in patients with negative surgical margins. Compared with patients treated by chemotherapy, the 4.1G high expression showed a better OS in those people who did not have chemotherapy. In contrast, the 4.1G high expression had a better OS in patients treated with radiotherapy than those without radiotherapy. All members were not significantly related to PPS and the 4.1N was associated with survival in patients who received treatments (*Tables 4-6*).

Discussion

4.1G is a membrane skeleton protein, which regulates cell adhesion, spreading, and migration of mouse embryonic fibroblasts through the β1 integrin pathway (11). Although the function of 4.1G is largely undetectable in tumors, based on previous studies, 4.1G protein has been confirmed to be related to the occurrence and development of tumors. There were 41% absence of 4.1G protein expression in ependymomas, and 4.1G deletions were associated with more aggressive clinical disease, encountered mostly by patients that either died of their tumor or had residual/recurrent tumor at last follow-up (12). However, there is few researches about the 4.1 family in the process of NSCLC. Our results revealed that 4.1G is the most prognostically valuable in lung cancer compared to several other family members. No matter in patients with NSCLC or adenocarcinoma lung cancer, excessive 4.1G expression showed protective potential, especially in female. What's more, in those patients who received surgical treatment with radiotherapy and negative margins which influenced by the surgeon's proficiency in a degree, 4.1G overexpression leaded to a better OS, which also can be observed in people without chemotherapy treatment.

4.1B, as an adaptor protein, located at the junction of cells, can link the cytoplasmic membrane to the cytoskeleton or cytoplasmic effector molecules, and can be involved in modulating cell growth, motility, adhesion, cytoskeleton organization (13). DAL-1 is a short form of 4.1B and contains the major functional structure of protein 4.1B. In recent years, several studies have confirmed that 4.1B, which is considered as a potential negative regulator, is closely connected with the occurrence and development of tumors (7,14,15). However, the controversy still exists. To date, the biological functions of protein 4.1B in carcinogenesis remain unknown. Yi *et al*. (16). demonstrated

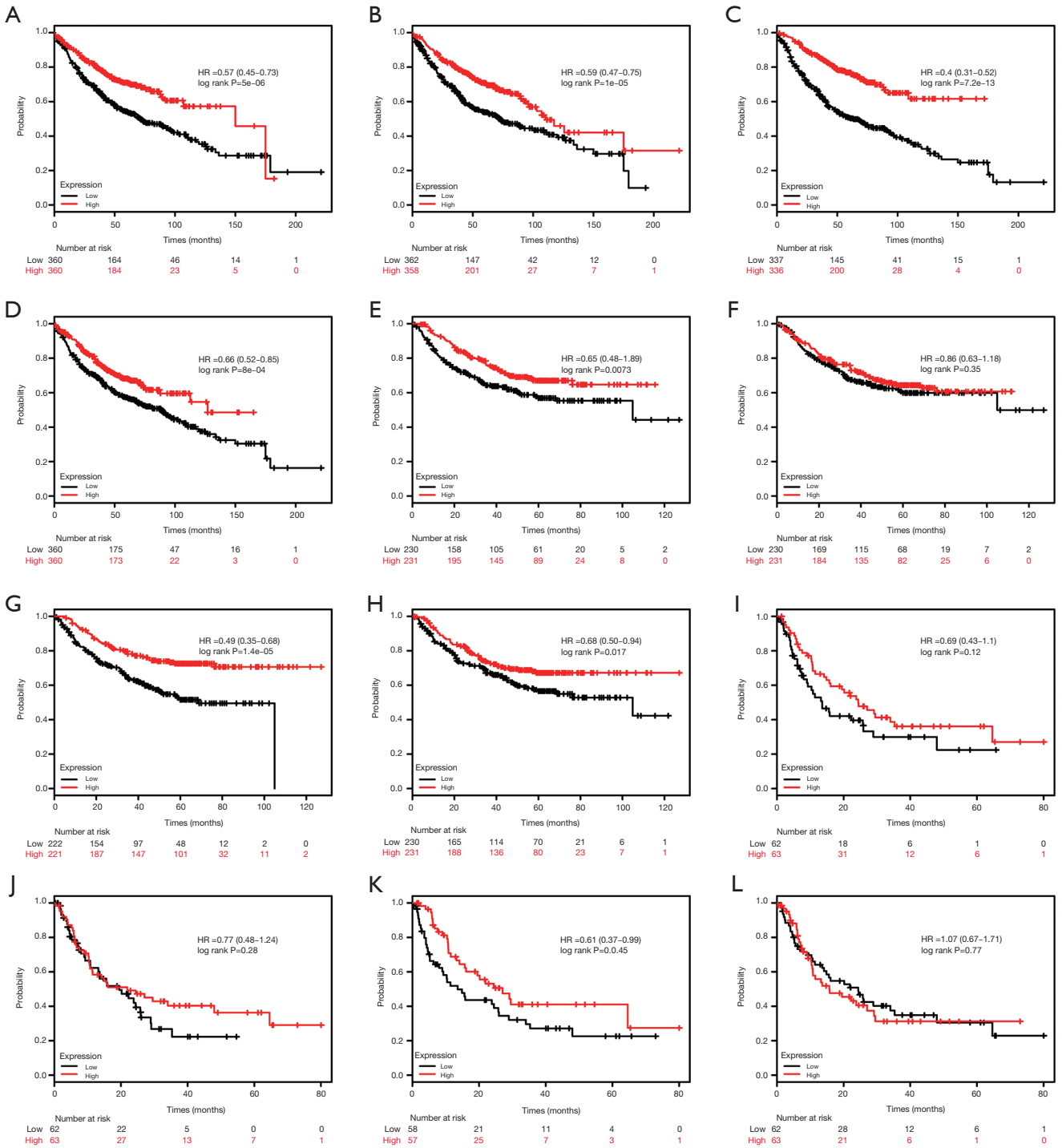

Figure 3 The prognostic roles of 4.1 in adenocarcinoma. (A,B,C,D) The relationship of 4.1G, 4.1B, 4.1R, 4.1N with OS. (E,F,G,H) The relationship of 4.1G, 4.1B, 4.1R, 4.1N with FP. (I,J,K,L) The relationship of 4.1G, 4.1B, 4.1R, 4.1N with PPS. HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; FP, first progression; PPS, post progression survival.

Table 1 Prognostic values of 4.1 members in gender

Gene	Affymetrix IDs	Outcome	Gender	Cases	HR	95% CI	P value
4.1G	201719_s_at	OS	Female	715	0.58	0.46–0.74	5.6e–06
			Male	1,100	0.85	0.73–1.00	0.048
4.1B	212681_at	OS	Female	715	0.81	0.64–1.02	0.077
			Male	1,100	0.88	0.75–1.03	0.1
4.1R	225051_at	OS	Female	375	0.46	0.32–0.66	1.1e–05
			Male	659	0.73	0.60–0.90	0.003
4.1N	212339_at	OS	Female	715	0.83	0.66–1.05	0.13
			Male	1,100	0.79	0.68–0.93	0.0043
4.1G	201719_s_at	FP	Female	468	0.68	0.51–0.91	0.0082
			Male	514	0.79	0.61–1.02	0.065
4.1B	212681_at	FP	Female	468	0.77	0.58–1.03	0.079
			Male	514	0.80	0.62–1.04	0.097
4.1R	225051_at	FP	Female	253	0.54	0.34–0.85	0.0073
			Male	343	0.55	0.39–0.77	0.00052
4.1N	212339_at	FP	Female	468	0.97	0.73–1.30	0.86
			Male	514	0.94	0.73–1.22	0.66
4.1G	201719_s_at	PPS	Female	175	0.68	0.47–0.99	0.045
			Male	179	0.92	0.65–1.29	0.63
4.1B	212681_at	PPS	Female	165	0.78	0.53–1.13	0.19
			Male	179	0.99	0.70–1.39	0.94
4.1R	225051_at	PPS	Female	56	0.58	0.28–1.22	0.15
			Male	82	0.47	0.27–0.81	0.0056
4.1N	212339_at	PPS	Female	165	0.96	0.66–1.39	0.82
			Male	179	0.89	0.63–1.26	0.51

HR, hazard ratio; CI, confidence interval; OS, overall survival; FP, first progression; PPS, post progression survival.

that the 4.1B was not required for normal development and 4.1B/DAL-1 did not function as a tumor suppressor gene. Our results revealed that high level 4.1B was linked to better OS, FP, and had advantages in those people who received surgical treatment with negative margins. All these indicates that 4.1B was a negative regulator in NSCLC, which was of significant value for prognosis.

Tran *et al.* (17) reported that 54% NSCLC showed greatly reduced levels of DAL-1 message, which had no significant differences among adenocarcinomas, squamous, large cell and non-specified NSCLCs. The results of our study showed that whether in squamous cell carcinoma and adenocarcinoma, high expression of 4.1B was correlated with better OS, which corroborated the results of Tran *et al.* Shinji Kikuchi reported that the methylation was found in 57% of primary NSCLC and it seemed to be a relatively early event in squamous cell carcinomas, but a late event in adenocarcinoma (18). Loss of DAL-1 expression led by the methylation was also demonstrated to be an important event in the pathogenesis of NSCLC (19). Furthermore, smoking was linked primarily to lung cancer in 90% of men and 70–80% of women with lung cancer, which may cause changes in the DNA methylation and gene expression associated with cancer (20). In those patients who never smoked, we reported that high expression

Table 2 The relationship between prognosis of 4.1 members and smoking status

Gene	Affymetrix IDs	Outcome	Smoking status	Cases	HR	95% CI	P value
4.1G	201719_s_at	OS	Smoked	820	0.72	0.58–0.89	0.0019
			Never smoked	205	0.32	0.17–0.59	0.00012
4.1B	212681_at	OS	Smoked	820	0.91	0.74–1.12	0.39
			Never smoked	205	0.35	0.19–0.64	0.00034
4.1R	225051_at	OS	Smoked	300	0.51	0.33–0.78	0.0014
			Never smoked	141	0.30	0.12–0.76	0.0067
4.1N	212339_at	OS	Smoked	820	1.04	0.85–1.28	0.68
			Never smoked	205	1.04	0.59–1.81	0.9
4.1G	201719_s_at	FP	Smoked	603	0.76	0.59–0.97	0.026
			Never smoked	193	0.42	0.25–0.69	0.00046
4.1B	212681_at	FP	Smoked	603	0.87	0.68–1.11	0.26
			Never smoked	193	0.49	0.30–0.80	0.0037
4.1R	225051_at	FP	Smoked	297	0.68	0.45–1.00	0.051
			Never smoked	141	0.38	0.20–0.73	0.0028
4.1N	212339_at	FP	Smoked	603	1.16	0.91–1.47	0.24
			Never smoked	193	0.63	0.38–1.02	0.056
4.1G	201719_s_at	PPS	Smoked	254	0.86	0.65–1.15	0.32
			Never smoked	67	0.35	0.18–0.67	0.00095
4.1B	212681_at	PPS	Smoked	254	1.07	0.8–1.42	0.66
			Never smoked	67	0.62	0.33–1.17	0.13
4.1R	225051_at	PPS	Smoked	96	0.59	0.36–0.98	0.04
			Never smoked	40	1.20	0.49–2.93	0.69
4.1N	212339_at	PPS	Smoked	254	0.87	0.65–1.16	0.34
			Never smoked	67	2.40	1.24–4.64	0.0073

HR, hazard ratio; CI, confidence interval; OS, overall survival; FP, first progression; PPS, post progression survival.

of 4.1B led to better OS and FP, which may be associated with the methylation caused by smoking.

Similar to 4.1B, 4.1N can connect transmembrane proteins to the actin cytoskeleton, which plays a vital role in maintaining the stability and integrity of cell membrane. The research on 4.1N is mostly focused on the nervous system, whereas it has also been reported that the expression level of 4.1N is closely related to the metastasis of tumors (21). Ji *et al.* (22) reintroduced the 4.1N-deleted breast cancer cell line by transfection with the pEGFP-4.1N plasmid, which subsequently reduced breast cancer cell adhesion, invasion, and migration significantly. In addition to this, 4.1N reversed epithelial-mesenchymal transition in ovarian cancer by inhibiting the expression of hypoxia-inducible factor HIF-1α, and highlighted its potential role in epithelial ovarian cancer (EOC) therapy as an inhibitor of hypoxia-induced tumor progression in EOC cells (23). 4.1N is also proved to be involved in the suppression of cell proliferation and migration through a flotillin-1/β-catenin/Wnt pathway in NSCLC (24). The data of our study revealed that 4.1N had a certain value in the prognosis of NSCLC. Highly expressed 4.1N showed better OS, especially in adenocarcinoma, and better FP. Compared with female, overexpression of 4.1N had a prognostic advantage

Table 3 The relationship between prognosis of 4.1 members and tumor stage

Gene	Affymetrix IDs	Stage	Cases	HR	95% CI	P value
4.1G	201719_s_at	Stage I	577	0.46	0.34–0.61	3.3e–08
		Stage II	244	0.65	0.45–0.94	0.023
		Stage III	70	1.42	0.83–2.44	0.20
4.1B	212681_at	Stage I	577	0.58	0.44–0.76	6.1e–05
		Stage II	244	0.63	0.44–0.91	0.013
		Stage III	70	0.88	0.51–1.52	0.65
4.1R	225051_at	Stage I	449	0.28	0.20–0.41	3.6e–13
		Stage II	161	0.61	0.38–0.96	0.032
		Stage III	44	0.91	0.46–1.80	0.78
4.1N	212339_at	Stage I	577	0.56	0.42–0.74	3.6e–05
		Stage II	244	0.95	0.65–1.37	0.77
		Stage III	70	0.89	0.52–1.53	0.67

HR, hazard ratio; CI, confidence interval.

Table 4 OS of 4.1 expression in treatment

Gene	Affymetrix IDs	Treatment	Cases	HR	95% CI	P value
4.1G	201719_s_at	Surgery (surgical margins negative)	726	0.67	0.53–0.84	6e–04
		Chemotherapy: no	310	0.70	0.50–0.98	0.037
		Chemotherapy: yes	176	1.04	0.69–1.56	0.86
		Radiotherapy: no	276	0.71	0.49–1.01	0.059
		Radiotherapy: yes	70	0.58	0.34–1.00	0.046
4.1B	212681_at	Surgery (surgical margins negative)	726	0.74	0.59–0.93	0.01
		Chemotherapy: no	310	1.12	0.80–1.57	0.50
		Chemotherapy: yes	176	0.88	0.59–1.32	0.55
		Radiotherapy: no	271	1.24	0.87–1.76	0.24
		Radiotherapy: yes	70	1.44	0.84–2.45	0.18
4.1R	225051_at	Surgery (surgical margins negative)	204	0.17	0.06–0.44	3.4e–05
		Chemotherapy: no	21	2.02	0.37–11.10	0.41
		Chemotherapy: yes	34	0.75	0.24–2.41	0.63
4.1N	212339_at	Surgery (surgical margins negative)	726	1.09	0.87–1.37	0.46
		Chemotherapy: no	310	0.99	0.71–1.38	0.94
		Chemotherapy: yes	176	0.97	0.65–1.45	0.88
		Radiotherapy: no	271	1.18	0.83–1.68	0.36
		Radiotherapy: yes	0.78	1.44	0.45–1.32	0.35

HR, hazard ratio; CI, confidence interval; OS, overall survival.

Table 5 FP of 4.1 expression in treatment

Gene	Affymetrix IDs	Treatment	Cases	HR	95% CI	P value
4.1G	201719_s_at	Surgery (surgical margins negative)	560	0.57	0.44–0.74	1.3e–05
		Chemotherapy: no	258	0.70	0.47–1.03	0.069
		Chemotherapy: yes	125	1.21	0.80–1.82	0.37
		Radiotherapy: no	259	0.75	0.51–1.10	0.14
		Radiotherapy: yes	68	0.76	0.45–1.29	0.31
4.1B	212681_at	Surgery (surgical margins negative)	560	0.65	0.50–0.83	0.00063
		Chemotherapy: no	258	1.11	0.75–1.64	0.59
		Chemotherapy: yes	125	0.97	0.64–1.47	0.89
		Radiotherapy: no	259	0.95	0.65–1.39	0.79
		Radiotherapy: yes	68	0.86	0.51–1.47	0.58
4.1R	225051_at	Surgery (surgical margins negative)	204	0.24	0.13–0.45	1.2e–06
		Chemotherapy: no	21	1.99	0.58–6.87	0.27
		Chemotherapy: yes	34	0.75	0.28–2.03	0.57
4.1N	212339_at	Surgery (surgical margins negative)	560	1.04	0.81–1.33	0.76
		Chemotherapy: no	258	0.92	0.62–1.35	0.67
		Chemotherapy: yes	125	1.17	0.77–1.78	0.45
		Radiotherapy: no	259	0.94	0.65–1.38	0.76
		Radiotherapy: yes	68	0.73	0.43–1.24	0.24

HR, hazard ratio; CI, confidence interval; FP, first progression.

in male. However, in those patients who never smoked, an excessively high 4.1N showed worse PPS. What's more, 4.1N did not show prognostic value in treatment.

4.1R acts as a multifunctional component of erythrocyte membrane and regulates the junctions of the RBC transmembrane proteins and the spectrin-actin cytoskeleton network (25). Mutations or defects in 4.1R cause instability of the network and consequently the whole cell membrane. 4.1R has been reported to play a number of essential roles. In the gastric epithelial cells, 4.1R associates with adherent junction protein β-catenin (26). Structural protein 4.1R is also integrally involved in nuclear envelope protein localization, centrosome-nucleus association and transcriptional signaling (27). Kang *et al*. reported that 4.1R negatively regulated T-cell activation by inhibiting the phosphorylation of LAT in mouse $CD4^+$ T lymphocytes (28). Even though, the specific mechanism of 4.1R in tumors still remains unclear, 4.1R had been confirmed to be closely linked to cell migration, and research showed that 40% of meningioma patients were lack of 4.1R expression (29,30). The results of our study found that 4.1R overexpression was associated with OS, FP, and PPS in NSCLC, especially in adenocarcinoma and men, in which the prognosis of 4.1R was most valuable. However, there was still controversy regarding the prognosis of smoking status. Highly expressed 4.1R had a better FP in non-smoking populations, while a better PPS in smoking population. Although there was no significant correlation between the prognosis of patients receiving chemotherapy and radiotherapy, the results also showed that the high expression of 4.1R was related to patients who received surgical treatment with margins negative.

Conclusions

We used KM plotter to evaluate the prognostic value of the 4.1 family mRNA expression in NSCLC patients. Even though all 4 family members were associated with the prognosis of NSCLC, the prognostic value should be combined with clinical characteristics and further evaluated in clinical studies. 4.1 proteins, as protective factor for

Table 6 PPS of 4.1 expression in treatment

Gene	Affymetrix IDs	Treatment	Cases	HR	95% CI	P value
4.1G	201719_s_at	Surgery (surgical margins negative)	246	0.75	0.55–1.01	0.054
		Chemotherapy: no	97	0.89	0.55–1.42	0.61
		Chemotherapy: yes	88	0.94	0.59–1.50	0.80
		Radiotherapy: no	104	0.86	0.55–1.34	0.51
		Radiotherapy: yes	57	0.72	0.40–1.29	0.27
4.1B	212681_at	Surgery (surgical margins negative)	246	0.94	0.70–1.27	0.69
		Chemotherapy: no	97	1.31	0.82–2.08	0.26
		Chemotherapy: yes	88	1.21	0.76–1.95	0.42
		Radiotherapy: no	104	1.03	0.67–1.60	0.89
		Radiotherapy: yes	57	1.68	0.93–3.01	0.081
4.1R	225051_at	Surgery (surgical margins negative)	56	1.29	0.62–2.68	0.50
		Chemotherapy: no	9	–	–	–
		Chemotherapy: yes	14	–	–	–
4.1N	212339_at	Surgery (surgical margins negative)	246	1.03	0.76–1.38	0.87
		Chemotherapy: no	97	0.83	0.52–1.33	0.45
		Chemotherapy: yes	88	0.77	0.48–1.24	0.28
		Radiotherapy: no	104	0.78	0.50–1.22	0.27
		Radiotherapy: yes	57	0.87	0.49–1.56	0.64

PPS, post progression survival.

cancer treatment, however, the mechanism of 4.1 family in NSCLC is still unclear. Our study was supposed to provide a reference for the prognosis of NSCLC and a potential therapeutic target and contribute to the development of new drugs for NSCLC.

Acknowledgments

Funding: Zhejiang Provincial Program for the Cultivation of High-Level Innovative Health Talents (Shanming Ruan, No. 2015-43, http://www.zjwjw.gov.cn/); Program for the Cultivation of Youth talents in China Association of Chinese Medicine (Shanming Ruan, No. QNRC2-C08, http://www.cacm.org.cn/); Zhejiang Provincial Program for the Cultivation of the Young and Middle-Aged Academic Leaders in Colleges and Universities (Shanming Ruan, No. 2017-248, http://www.zjedu.gov.cn/); Zhejiang Provincial Project for the key discipline of Traditional Chinese Medicine (Yong Guo, No. 2017-XK-A09, http://www.zjwjw.gov.cn/).

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-2501

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2501). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All data in the database is publicly available and exempt from Institutional Review Board review.

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Cite this article as: Xiang Y, Shan F, Feng G, Guo K, Ruan S, Huang D. The prognostic value of 4.1 mRNA expression in non-small cell lung cancer. Transl Cancer Res 2021;10(3):1216-1228. doi: 10.21037/tcr-20-2501

